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(54) Title: 5-ARYLINDOLE DERIVATIVES			
(57) Abstract			
<p>Compounds of formula (I), wherein A, B, D, E, and F are each independently nitrogen or carbon; R<sub>1</sub> is hydrogen, C<sub>1</sub> to C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>R<sub>7</sub>, or C<sub>1</sub> to C<sub>3</sub> alkyl-aryl; R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are each independently hydrogen, C<sub>1</sub> to C<sub>6</sub> alkyl, aryl, C<sub>1</sub> to C<sub>3</sub> alkyl-aryl, halogen, cyano, nitro, -(CH<sub>2</sub>)<sub>m</sub>NR<sub>8</sub>R<sub>9</sub>, -(CH<sub>2</sub>)<sub>m</sub>OR<sub>9</sub>, -SR<sub>9</sub>, -SO<sub>2</sub>NR<sub>8</sub>R<sub>9</sub>, -(CH<sub>2</sub>)<sub>m</sub>NR<sub>8</sub>SO<sub>2</sub>R<sub>9</sub>, -(CH<sub>2</sub>)<sub>m</sub>NR<sub>8</sub>CO<sub>2</sub>R<sub>9</sub>, -(CH<sub>2</sub>)<sub>m</sub>NR<sub>8</sub>COR<sub>9</sub>, -(CH<sub>2</sub>)<sub>m</sub>CONR<sub>7</sub>R<sub>9</sub>, or -(CH<sub>2</sub>)<sub>m</sub>CO<sub>2</sub>R<sub>9</sub>; R<sub>7</sub> and R<sub>8</sub>, R<sub>3</sub> and R<sub>4</sub>, R<sub>4</sub> and R<sub>5</sub>, and R<sub>5</sub> and R<sub>6</sub> may be taken together to form a 5- to 7-membered heteroaryl ring having 1 or 2 heteroatoms of N, O, or S; R<sub>7</sub> is -OR<sub>10</sub>, -SR<sub>10</sub>, -SO<sub>2</sub>NR<sub>10</sub>R<sub>11</sub>, -NR<sub>10</sub>SO<sub>2</sub>R<sub>11</sub>, -NR<sub>10</sub>CO<sub>2</sub>R<sub>11</sub>, -NR<sub>10</sub>COR<sub>11</sub>, -CONR<sub>10</sub>R<sub>11</sub>, or -CO<sub>2</sub>R<sub>10</sub>; R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub> and R<sub>11</sub> are each independently hydrogen, C<sub>1</sub> to C<sub>6</sub> alkyl, or C<sub>1</sub> to C<sub>3</sub> alkyl-aryl; m is 0, 1, or 2; n is 2, 3, or 4; and the above aryl groups and the aryl moieties of the above alkyl-aryl groups are each independently phenyl or substituted phenyl, wherein said substituted phenyl may be substituted with 1 to 3 of C<sub>1</sub> to C<sub>4</sub> alkyl, halogen, hydroxy, cyano, carboxamido, nitro, or C<sub>1</sub> to C<sub>4</sub> alkoxy, and the pharmaceutically acceptable salts thereof. These compounds are useful in treating migraine and other disorders and are new. These compounds are useful psychotherapeutics and are potent serotonin (5-HT<sub>1</sub>) agonists and may be used in the treatment of depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain, and chronic paroxysmal hemicrania and headache associated with vascular disorders, and other disorders arising from deficient serotonergic neurotransmission. The compounds can also be used as centrally acting antihypertensives and vasodilators.</p>			

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**5-ARYLINDOLE DERIVATIVES****Background of the Invention**

The present invention relates to indole derivatives, to processes and intermediates for their preparation, to pharmaceutical compositions containing them and to their medicinal use. The active compounds of the present invention are useful in  
10 treating migraine and other disorders.

United States Patents 4,839,377 and 4,855,314 and European Patent Application Publication Number 313397 refer to 5-substituted 3-aminoalkyl indoles. The compounds are said to be useful for the treatment of migraine.

British Patent Application 040279 refers to 3-aminoalkyl-1H-indole-5-thioamides  
15 and carboxamides. The compounds are said to be useful in treating hypertension, Raymond's disease and migraine.

European Patent Application Publication Number 303506 refers to 3-poly:hydro-pyridyl-5-substituted-1H-indoles. The compounds are said to have 5-HT<sub>1</sub> receptor agonist and vasoconstrictor activity and to be useful in treating migraine.

20 European Patent Application Publication Number 354777 refers to N-piperidinyli:indolyl:ethyl-alkane sulfonamide derivatives. The compounds are said to have 5-HT<sub>1</sub> receptor agonist and vasoconstrictor activity and to be useful in treating cephalic pain.

European Patent Application Publication Numbers 438230, 494774, and 497512  
25 refers to indole-substituted five-membered heteroaromatic compounds. The compounds are said to have 5-HT<sub>1</sub>-like receptor agonist activity and to be useful in the treatment of migraine and other disorders for which a selective agonist of these receptors is indicated.

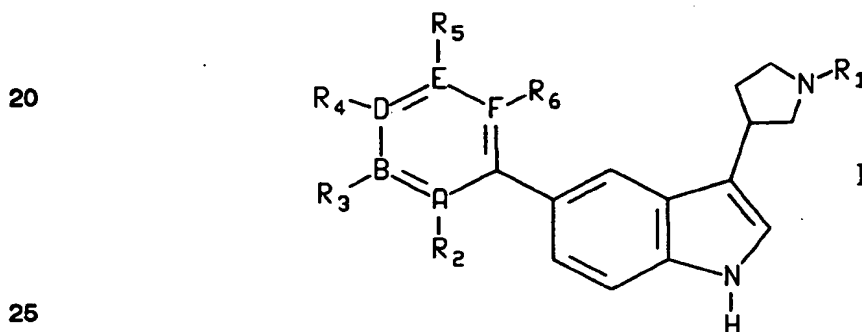
European Patent Application Publication Number 313397 refers to 5-heterocyclic  
30 indole derivatives. The compounds are said to have exceptional properties for the treatment and prophylaxis of migraine, cluster headache, and headache associated with vascular disorders. These compound are also said to have exceptional "5-HT<sub>1</sub>-like" receptor agonism.

International Patent Application PCT/GB91/00908 and International Patent  
35 Application WO 91/18897 refers to 5-heterocyclic indole derivatives. The compounds are said to have exceptional properties for the treatment and prophylaxis of migraine,

European Patent Application Publication Number 497512 A2 refers to a class of imidazole, triazole, and tetrazole derivatives which are selective agonists for 5-HT<sub>1</sub>-like receptors. These compounds are said to be useful for treating migraine and associated disorders.

Y. Yang, et. al describe the synthesis of 5-arylindoles in Heterocycles, Vol. 34, 15 1395 (1992) via palladium catalyzed cross-coupling reactions.

**The present invention relates to compounds of the formula**



wherein A, B, D, E, and F are each independently nitrogen or carbon; R<sub>1</sub> is hydrogen, C<sub>1</sub> to C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>R<sub>7</sub>, or C<sub>1</sub> to C<sub>3</sub> alkyl-aryl; R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are each independently hydrogen, C<sub>1</sub> to C<sub>6</sub> alkyl, aryl, C<sub>1</sub> to C<sub>3</sub> alkyl-aryl, halogen (e.g. fluorine, chlorine, bromine or iodine), cyano, nitro, -(CH<sub>2</sub>)<sub>m</sub>NR<sub>8</sub>R<sub>9</sub>, -(CH<sub>2</sub>)<sub>m</sub>OR<sub>9</sub>, -SR<sub>9</sub>, -SO<sub>2</sub>NR<sub>8</sub>R<sub>9</sub>, -(CH<sub>2</sub>)<sub>m</sub>NR<sub>8</sub>SO<sub>2</sub>R<sub>9</sub>, -(CH<sub>2</sub>)<sub>m</sub>NR<sub>8</sub>CO<sub>2</sub>R<sub>9</sub>, -(CH<sub>2</sub>)<sub>m</sub>NR<sub>8</sub>COR<sub>9</sub>, -(CH<sub>2</sub>)<sub>m</sub>CONR<sub>7</sub>R<sub>8</sub>, or -(CH<sub>2</sub>)<sub>m</sub>CO<sub>2</sub>R<sub>9</sub>; R<sub>2</sub> and R<sub>3</sub>, R<sub>3</sub> and R<sub>4</sub>, R<sub>4</sub> and R<sub>5</sub>, and R<sub>5</sub> and R<sub>6</sub> may be taken together to form a five- to seven-membered alkyl ring, a six-membered aryl ring, a five- to seven-

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membered heteroalkyl ring, having 1 heteroatom of N, O, or S, or a five- to six-membered heteroaryl ring having 1 or 2 heteroatoms of N, O, or S;  $R_7$  is  $OR_{10}$ ,  $-SR_{10}$ ,  $-SO_2NR_{10}R_{11}$ ,  $-NR_{10}SO_2R_{11}$ ,  $-NR_{10}CO_2R_{11}$ ,  $-NR_{10}COR_{11}$ ,  $-CONR_{10}R_{11}$ , or  $-CO_2R_{10}$ ;  $R_8$ ,  $R_9$ ,  $R_{10}$  and  $R_{11}$  are independently hydrogen,  $C_1$  to  $C_6$  alkyl, or  $C_1$  to  $C_3$  alkyl-aryl;  $m$  is 0, 1, or 2;  $n$  is 2, 3, or 4; and the above aryl groups and the aryl moieties of the above alkyl-aryl groups are each independently phenyl or substituted phenyl, wherein said substituted phenyl may be substituted with one to three of  $C_1$  to  $C_4$  alkyl, halogen (e.g. fluorine, chlorine bromine or iodine), hydroxy, cyano, carboxamido, nitro, or  $C_1$  to  $C_4$  alkoxy, and the pharmaceutically acceptable salts thereof. These compounds are potent 5-HT<sub>1D</sub> agonists with selectivity for the 5-HT<sub>1D</sub> receptor and are useful in treating migraine and other disorders.

The compounds of the invention include all optical isomers of formula I (e.g. R and S stereogenicity at any chiral site) and their racemic, diastereomeric, or epimeric mixtures.

Unless otherwise indicated, the alkyl and alkenyl groups referred to herein, as well as the alkyl moieties of other groups referred to herein (e.g. alkoxy), may be linear or branched, and they may also be cyclic (e.g. cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl) or be linear or branched and contain cyclic moieties.

Preferred compounds of the invention are compounds of the formula I wherein B or E is nitrogen; A or F is carbon;  $R_1$  is hydrogen,  $C_1$  to  $C_3$  alkyl, or  $-(CH_2)_2OCH_3$ .

The following compounds are particularly preferred:

3-(N-methylpyrrolidin-3-yl)-5-(pyrimid-5-yl)-1H-indole;

5-(pyrimid-5-yl)-3-(pyrrolidin-3-yl)-1H-indole;

3-[N-(2-methoxyethyl)pyrrolidin-3-yl]-5-(pyrimid-5-yl)-1H-indole;

3-(N-ethylpyrrolidin-3-yl)-5-(pyrimid-5-yl)-1H-indole;

5-(3-cyanopyrid-5-yl)-3-(N-methylpyrrolidin-3-yl)-1H-indole;

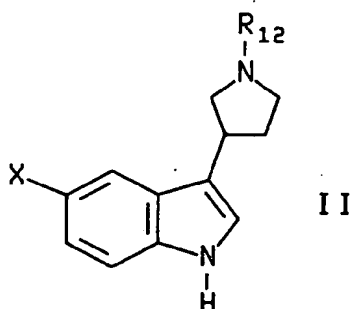
5-(3-cyanopyrid-5-yl)-3-(pyrrolidin-3-yl)-1H-indole;

5-(3-cyanopyrid-5-yl)-1H-3-[N-(2-methoxyethyl)pyrrolidin-3-yl]-indole; and

3-(N-methylpyrrolidin-3-yl)-5-(1,2,4-triazin-3-yl)-1H-indole.

The present invention also relates to a compound of the formula

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wherein X is halogen [chloride, bromide, iodide] or  $-\text{OSO}_2\text{CF}_3$  and  $\text{R}_{12}$  is hydrogen, methyl, or benzyl. These compounds are useful as intermediates in preparing compounds of formula I.

15 The present invention also relates to a pharmaceutical composition for treating a condition selected from hypertension, depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain, and chronic paroxysmal hemicrania and headache associated with vascular disorders comprising an amount of a compound of the formula I or a pharmaceutically acceptable salt thereof effective in treating such condition and a pharmaceutically acceptable carrier.

20 The present invention also relates to a method for treating a condition selected from hypertension, depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain and chronic paroxysmal hemicrania and headache associated with vascular disorders comprising administering to a mammal (e.g., a human) requiring such treatment an amount of a compound of the formula I or a pharmaceutically acceptable salt thereof effective in treating such condition.

25 The present invention also relates to a method for treating disorders arising from deficient serotonergic neurotransmission (e.g., depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain and chronic paroxysmal hemicrania and headache associated with vascular disorders) comprising administering to a mammal (e.g., a human) requiring such treatment an amount of a compound of the formula I or a pharmaceutically acceptable salt thereof effective in treating such condition.

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The present invention also relates to a method for treating disorders arising from deficient serotonergic neurotransmission (e.g., depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain and chronic paroxysmal hemicrania and headache associated with vascular disorders) comprising administering  
5 to a mammal (e.g., a human) requiring such treatment an amount of a compound of the formula I or a pharmaceutically acceptable salt thereof effective in treating such condition.

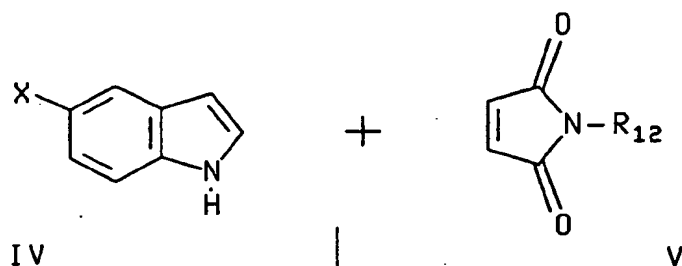
Detailed Description of the Invention

The compounds of formula I can be prepared via the following reaction scheme:

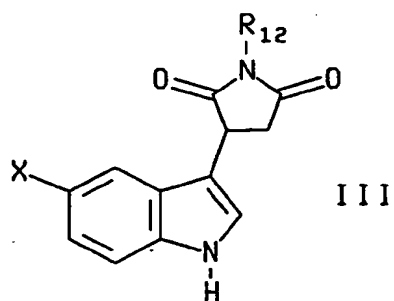
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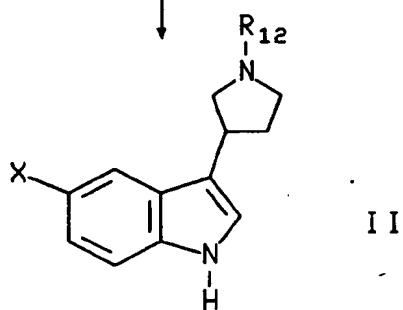


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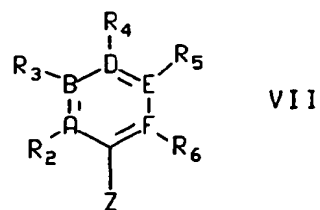


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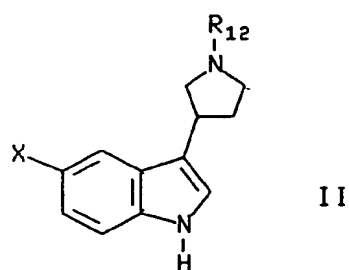


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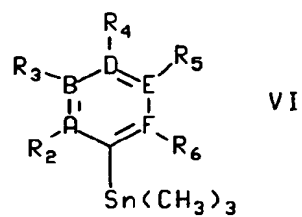
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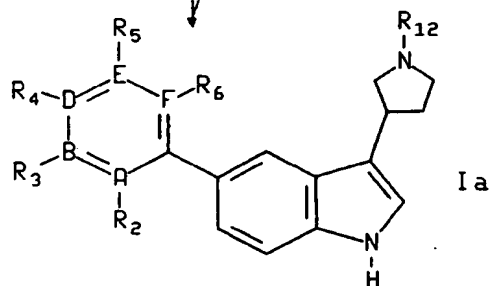
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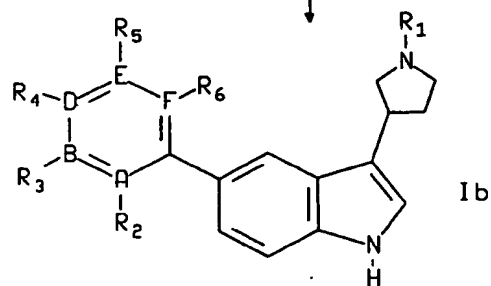
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Compounds of formula III wherein X is halogen [chloride, bromide, iodide] or -OSO<sub>2</sub>CF<sub>3</sub> and R<sub>1,2</sub> is hydrogen, methyl, or benzyl can be prepared from the condensation of a compound of formula IV wherein X is as defined above with a compound of formula V wherein R<sub>1,2</sub> is as defined above in an inert solvent. Suitable  
5 inert solvents include C<sub>1</sub> to C<sub>3</sub> alcohols, acetic acid, formic acid, and N,N-dimethylformamide. The preferred solvent is acetic acid. The reaction is usually conducted at a temperature of from about 65°C to about 154°C, preferably about 100°C to about 110°C.

Compounds of formula II wherein X and R<sub>1,2</sub> are as defined above can be  
10 prepared via the reduction of a compound of formula III wherein R<sub>1,2</sub> is as defined above in an inert solvent. Suitable reducing agents include lithium aluminum hydride, lithium borohydride, and diborane. Lithium aluminum hydride is the preferred reducing agent. Suitable inert solvents include tetrahydrofuran, dioxane, diethyl ether, and other ethers. Tetrahydrofuran is the preferred solvent. The reaction is usually conducted at a  
15 temperature of from about 25°C to about 100°C, preferably at about 65°C.

Compounds of formula VI wherein A, B, D, E, F, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are as defined above can be prepared from a compound of formula VII wherein A, B, D, E, F, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are as defined above, and Z is halogen [chloride, bromide, iodide] or -OSO<sub>2</sub>CF<sub>3</sub> via a transition metal catalyzed insertion reaction using  
20 hexamethylditin in an inert solvent, usually in the presence of a base, lithium chloride, and butylated hydroxytoluene [i.e., 2,6-di-~~tert~~-butyl-4-methylphenol, BHT]. Suitable catalysts are of palladium (II) and palladium (0) species, such as palladium (II) acetate, palladium (II) chloride, bis(triphenylphosphine)palladium (II) chloride, and tetrakis(triphenylphosphine)palladium(0). The preferred catalyst is  
25 tetrakis(triphenylphosphine)palladium(0). Suitable inert solvents include ethers, such as tetrahydrofuran and dioxane, acetonitrile, N,N-dimethylformamide, and N-methylpyrrolidin-2-one. Dioxane is the preferred inert solvent. Suitable bases include tertiary amines, sodium bicarbonate, and sodium carbonate. The preferred base is triethylamine. The reaction is usually conducted at a temperature between about 70°C  
30 and about 210°C, preferably between about 90°C and 154°C.

Compounds of formula Ia wherein A, B, D, E, F, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>1,2</sub> are as defined above can be prepared by the transition metal catalyzed aryl cross-coupling reaction between a compound of formula II wherein X and R<sub>1,2</sub> are as defined above

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and a compound of formula VI wherein A, B, D, E, F, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are as defined above in an inert solvent, usually in the presence of a base, lithium chloride, and butylated hydroxytoluene [i.e., 2,6-di-tert-butyl-4-methylphenol, BHT]. Suitable catalysts are palladium (II) and palladium (0) species, such as palladium (II) acetate, 5 palladium (II) chloride, bis(triphenylphosphine)palladium (II) chloride, tetrakis(triphenylphosphine)palladium(0). The preferred catalyst is bis(triphenylphosphine)palladium (II) chloride. Suitable inert solvents include acetonitrile, N,N-dimethylformamide, and N-methylpyrrolidin-2-one. N,N-dimethylformamide is the preferred inert solvent. Suitable bases include tertiary amines, sodium bicarbonate, and 10 sodium carbonate. The preferred base is triethylamine. The reaction is usually conducted at a temperature between about 70°C and about 210°C, preferably between about 90°C and 154°C.

Compounds of formula Ib wherein A, B, D, E, F, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are as defined above can be prepared from a compound of formula Ia wherein R<sub>12</sub> is 15 benzyl, and A, B, D, E, F, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are as defined above via a reductive amination using an aldehyde of the formula R<sub>13</sub>CHO, where R<sub>13</sub> is C<sub>1</sub> to C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>s</sub>R<sub>7</sub>, or C<sub>1</sub> to C<sub>2</sub> alkyl-aryl, s is 1, 2, or 3, and R<sub>7</sub> is as defined above, along with a transition metal catalyst, and a hydrogen source in an inert solvent. Suitable catalysts include palladium on carbon, Raney nickel, platinum oxide, and palladium hydroxide 20 on carbon. The preferred catalyst is palladium hydroxide on carbon. Suitable hydrogen sources include hydrogen gas, ammonium formate, and formic acid. Hydrogen gas at a pressure of from about one to about three atmospheres is the preferred hydrogen source. Three atmospheres of hydrogen gas is the preferred pressure. Suitable solvents include C<sub>1</sub> to C<sub>4</sub> alcohols, acetonitrile, N,N-dimethylformamide, and N-methylpyrrolidine. 25 Ethanol is the preferred solvent. The reaction is usually conducted at a temperature of from about 25°C to about 100°C, preferably about 25°C to about 50°C.

Compounds of formula IV, formula V, and formula VII are either commercially available or can be prepared using methods known to one skilled in the art. Aldehydes of the formula R<sub>13</sub>CHO wherein R<sub>13</sub> is as defined above are also either commercially 30 available or can be prepared using methods known to one skilled in the art.

Unless indicated otherwise, the pressure of each of the above reactions is not critical. Generally, the reactions will be conducted at a pressure of from about one to about three atmospheres, preferably at ambient pressure (about one atmosphere).

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The compounds of the formula I which are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the formula I from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent, and subsequently convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is obtained.

The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

Those compounds of the formula I which are also acidic in nature, e.g., where  $R_2$  contains a carboxylate, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particular, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the herein described acidic compounds of formula I. These non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide

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together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction of maximum product of yields of the desired final product.

5       The compounds of the formula I and the pharmaceutically acceptable salts thereof (hereinafter, also referred to as the active compounds of the invention) are useful psychotherapeutics and are potent serotonin (5-HT<sub>1</sub>) agonists with selectivity for the 5-HT<sub>1D</sub> receptor and may be used in the treatment of depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, chronic paroxysmal  
10   hemiplegia and headache associated with vascular disorders, pain, and other disorders arising from deficient serotonergic neurotransmission. The compounds can also be used as centrally acting antihypertensives and vasodilators. The active compounds of the invention can be evaluated as anti-migraine agents by testing the extent to which they mimic sumatriptan in contracting the dog isolated saphenous vein strip [P.P.A. Humphrey et al., Br. J. Pharmacol., 94, 1128 (1988)]. This effect can be blocked by  
15   methiothepin, a known serotonin antagonist. Sumatriptan is known to be useful in the treatment of migraine and produces a selective increase in carotid vascular resistance in the anesthetized dog. It has been suggested [W. Fenwick et al., Br. J. Pharmacol., 96, 83 (1989)] that this is the basis of its efficacy.

20       The active compounds of the present invention can also be evaluated via the plasma protein extravasation response within the dura mater of guinea pigs following unilateral electrical trigeminal ganglion stimulation, as described in Markowitz et al., J. Neurosci., 7 (12), 4129-4136 (1987). The extent to which they mimic sumatriptan, in terms of both potency and efficacy, is determined in this assay.

25       The serotonin 5-HT<sub>1</sub> agonist activity is measured in in vitro receptor binding assays as described for the 5-HT<sub>1A</sub> receptor using rat cortex as the receptor source and [<sup>3</sup>H]-8-OH-DPAT as the radioligand [D. Hoyer et al. Eur. J. Pharm., Vol. 118, 13 (1985)] and as described for the 5-HT<sub>1D</sub> receptor using bovine caudate as the receptor source and [<sup>3</sup>H]serotonin as the radioligand [R.E. Heuring and S.J. Peroutka, J. Neuroscience,  
30   Vol.7, 894 (1987)]. 5-HT agonist activity is defined by agents with affinities (IC<sub>50</sub>s) of 250nM or less at either binding assay.

The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active

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compounds of the invention may be formulated for oral, buccal, intranasal, parenteral (e.g., intravenous, intramuscular or subcutaneous) or rectal administration or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycolate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form e.g. in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or

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suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

10 A proposed dose of the active compounds of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above (e.g., migraine) is 0.1 to 200 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

15 Aerosol formulations for treatment of the conditions referred to above (e.g., migraine) in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains 20 $\mu$ g to 1000 $\mu$ g of the compound of the invention. The overall daily dose with an aerosol will be within the range 100  $\mu$ g to 10 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

20 The following Examples illustrate the preparation of the compounds of the present invention and are not intended to limit in any way the scope of the claims. Commercial reagents were utilized without further purification. Melting points are uncorrected. NMR data are reported in parts per million ( $\delta$ ) and are referenced to the deuterium lock signal from the sample solvent. Specific rotations were measured at room temperature using the sodium D line (589 nm). Unless otherwise stated, all mass spectrum were performed using electron impact (EI, 70 eV) conditions. Chromatography refers to column chromatography performed using 32-63 $\mu$ m silica gel and executed under nitrogen pressure (flash chromatography) conditions. Room temperature refers to 20-25°C.

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#### Example 1

##### 3-(N-Methylpyrrolidin-3-yl)-5-(pyrimid-5-yl)-1H-indole

A mixture of 5-bromo-3-(N-methylpyrrolidin-3-yl)-1H-indole (0.450 g, 1.86 mmol), 5-trimethylstannylpyrimidine (0.518 g, 1.86 mmol), bis(triphenylphosphine)palladium(II)

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chloride (0.100 g), triethylamine (0.84 mL, 6.03 mmol, 3.2 eq), lithium chloride (0.254 g), and 2,6-di-tert-butyl-4-methylphenol (3.0 g) in anhydrous N,N-dimethylformamide (8 mL) was heated at reflux under nitrogen for 4 hours. The resulting reaction mixture was evaporated under reduced pressure, and the residue was column chromatographed using silica gel (approximately 25 g) and elution with 9:1:0.1 [methylene chloride/methanol/ammonium hydroxide] afforded the title compound (0.089 g, 0.32 mmol, 17%) as an off-white solid: mp, 140.0-143.0°C; TLC  $R_f$  = 0.20 in 9:1:0.1 [methylene chloride/methanol/ammonium hydroxide];  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  9.05 (s, 2H), 9.03 (s, 1H), 7.87 (d,  $J$ =1.1 Hz, 1H), 7.47 (d,  $J$ =8.4 Hz, 1H), 7.39 (dd,  $J$ =1.6 and 8.5 Hz, 1H), 7.16 (s, 1H), 4.90 (s, 1 exchangeable H), 3.78-3.66 (m, 1H), 3.16 (t,  $J$ =8.7 Hz, 1H), 2.92-2.84 (m, 1H), 2.72-2.59 (m, 2H), 2.42 (s, 3H), 2.42-2.33 (m, 1H), 2.10-1.99 (m, 1H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  156.6, 155.9, 138.9, 137.7, 129.0, 125.4, 123.2, 121.4, 119.7, 118.7, 113.6, 63.5, 57.1, 42.6, 36.3, 33.2; FAB LRMS ( $m/z$ , relative intensity) 279 ( $[\text{MH}]^+$ , 100); HRMS calculated for  $\text{C}_{17}\text{H}_{18}\text{N}_4$ , 278.1533, found 278.1520.

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#### Example 2

##### 5-(5-Cyanopyrid-3-yl)-3-(N-methylpyrrolidin-3-yl)-1H-indole

A mixture of 5-bromo-3-(N-methylpyrrolidin-3-yl)-1H-indole (0.500 g, 1.79 mmol), 5-cyano-3-trimethylstannylpyridine (0.525 g, 1.97 mmol, 1.1 eq), bis(triphenylphosphine)palladium(II) chloride (0.628 g, 0.90 mmol, 0.5 eq), triethylamine (1.19 mL, 8.59 mmol, 4.8 eq), lithium chloride (0.235 g, 5.55 mmol, 3.1 eq), and 2,6-di-tert-butyl-4-methylphenol (40 mg) in anhydrous acetonitrile (5 mL) was heated at reflux under nitrogen for 20 hours. The resulting reaction mixture was evaporated under reduced pressure, and the residue was column chromatographed using silica gel (approx 50 g) and elution with 9:1:0.1 [methylene chloride/methanol/ammonium hydroxide] to afford the title compound (0.060 g, 0.20 mmol, 11%) as a clear, pale brown oil: LRMS ( $m/z$ , relative intensity) 302 ( $\text{M}^+$ , 29), 245 (8), 57 (100); HRMS calculated for  $\text{C}_{19}\text{H}_{18}\text{N}_4$ , 302.1528, found 302.1533.

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#### Example 3

##### 5-Bromo-3-(N-methylpyrrolidin-3-yl)-1H-indole

To a stirred mixture of lithium aluminum hydride (1.10 g, 29.0 mmol, 2.2 eq) in anhydrous tetrahydrofuran (60 mL) at 0°C was added 3-(5-bromoindol-3-yl)-N-methylsuccinimide (4.00 g, 13.02 mmol) portionwise cautiously. The resulting reaction mixture was heated at reflux under nitrogen for 2 hours. The reaction mixture was then

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cooled, and sodium sulfate decahydrate (approximately 20 g) was added slowly and cautiously, followed by the addition of water (approximately 2 mL) and ethyl acetate (200 mL). The resulting mixture was stirred at room temperature under nitrogen for 2 hours, and then filtered through Celite®. The filtrate was evaporated under reduced  
5 pressure to afford the title compound (2.64 g, 9.46 mmol, 73%) as an off-white solid: mp, 163.0-164.0°C; TLC  $R_f$  = 0.30 in 9:1:0.1 [methylene chloride/methanol/ammonium hydroxide];  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  11.0 (br m, NH), 7.74 (d,  $J$ =1.3 Hz, 1H), 7.29 (d,  $J$ =8.8 Hz, 1H), 7.20 (br s, 1H), 7.15 (dd,  $J$ =1.7 and 8.6 Hz, 1H), 3.55-3.45 (m, 1H), 2.88 (t,  $J$ =8.2 Hz, 1H), 2.62-2.42 (m, 3H), 2.29 (s, 3H), 2.28-2.21 (m, 1H), 1.90-1.80 (m, 1H);  
10  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  135.4, 128.2, 123.4, 122.9, 121.1, 118.3, 113.5, 110.8, 62.6, 56.0, 42.1, 34.4, 32.2; HMRS calculated for  $\text{C}_{13}\text{H}_{16}\text{BrN}_2$  278.0415, found 278.0355.

#### Example 4

##### 3-(5-Bromoindol-3-yl)-N-methylsuccinimide

A solution of 5-bromoindole (4.00 g, 20.40 mmol) and N-methylmaleimide (5.00  
15 g, 45.00 mmol, 2.2 eq) in glacial acetic acid (50 mL) was heated at reflux under nitrogen for 120 hours. The resulting reaction mixture was evaporated under reduced pressure, and the residue was stirred vigorously in a solution of ether/methylene chloride (9:1, 200 mL) for 2 hours. Undissolved solid was filtered to afford the title compound (4.34 g, 14.13 mmol, 69%) as a pale yellow solid: mp, 196.0-197.0°C; TLC  
20  $R_f$  = 0.3 in diethyl ether;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.35 (br m, NH), 7.56 (d,  $J$ =1.5 Hz, 1H), 7.29 (dd,  $J$ =1.7 and 8.6 Hz, 1H), 7.22 (d,  $J$ =8.7 Hz, 1H), 7.08 (br s, 1H), 4.26 (dd,  $J$ =5.1 and 9.4 Hz, 1H), 3.28 (dd,  $J$ =9.4 and 18.3 Hz, 1H), 3.11 (s, 3H), 2.87 (dd,  $J$ =5.1 and 18.3 Hz, 1H); FAB LRMS ( $m/z$ , relative intensity,  $\text{NH}_4^+$  as ionization source) 326 ([ $\text{M}(\text{with } ^{81}\text{Br})\text{-NH}_4$ ] $^+$ , 100), 324 ([ $\text{M}(\text{with } ^{79}\text{Br})\text{-NH}_4$ ] $^+$ , 96), 309 ([ $\text{M}(\text{with } ^{81}\text{Br})\text{-H}$ ] $^+$ , 21),  
25 307 ([ $\text{M}(\text{with } ^{79}\text{Br})\text{-H}$ ] $^+$ , 20). Anal. calcd for  $\text{C}_{13}\text{H}_{11}\text{BrN}_2\text{O}_2$ : C, 50.84; H, 3.61; N, 9.12. Found: C, 50.67; H, 3.43; N, 9.00.

#### Example 5

##### 5-Trimethylstannylpyrimidine

A mixture of 5-bromopyrimidine (4.00 g, 25.16 mmol), hexamethylditin (9.06 g,  
30 27.67 mmol, 1.1 eq), lithium chloride (1.27 g, 30.19 mmol, 1.2 eq) tetrakis(triphenylphosphine)palladium(0) (1.13 g, 0.98 mmol, 0.04 eq), and 2,6-di-*tert*-butyl-4-methylphenol (0.08 g) in anhydrous 1,4-dioxane (45 mL) has heated at reflux under nitrogen for 16 hours. The resultant reaction mixture was evaporated under reduced

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pressure, and the residue was directly column chromatographed using silica gel (approximately 250 g) and elution with ethyl acetate/hexanes (1:1) to afford the title compound (4.75 g, 19.6 mmol, 78%) as a clear, pale yellow liquid: TLC  $R_f$  = 0.6 in 1:1 ethyl acetate/hexanes;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.11 (s, 1H), 8.70 (s, 2H), 0.38 (s, 9H).

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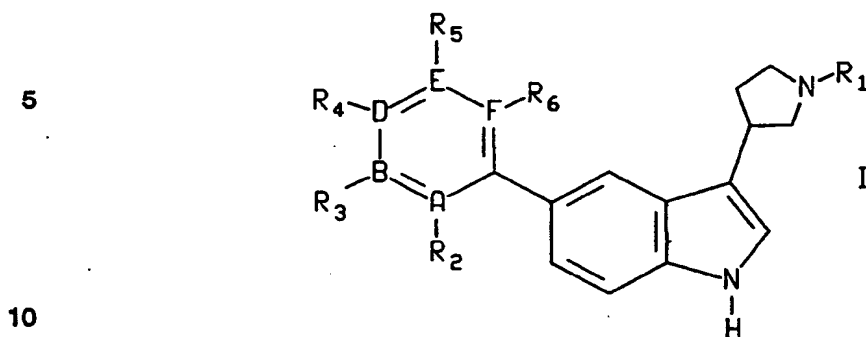
Example 65-Cyano-3-trimethylstannylpyridine

A mixture of 3-bromo-5-cyanopyridine (0.58 g, 3.17 mmol) [C. Zwart and J.P. Wibaut, Rec. trav. chim., 74, 1062 (1955)], lithium chloride (0.161 g, 3.80 mmol, 1.2 eq), 2,6-di-tert-butyl-4-methylphenol (12mg), tetrakis(triphenylphosphine)palladium(0) (0.145 g, 0.13 mmol, 0.04 eq), and hexamethylditin (1.14 g, 3.49 mmol, 1.1 eq) in anhydrous dioxane (6 mL) was heated at reflux under nitrogen for 4.5 hours. The resulting reaction mixture was evaporated under reduced pressure, and the residue was column chromatographed using silica gel (approx 50 g) and elution with 3:1 [hexanes/ether] to afford the title compound (0.68 g, 2.55 mmol, 80%) as a white solid: mp, 77.0-79.0°C; 10 IR (KBr) 2231  $\text{cm}^{-1}$ ;  $R_f$  = 0.4 in diethyl ether;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.79-8.77 (m, 2H), 8.01 (dd,  $J$ =2.1 and 1.5 Hz, 1H), 0.38 (s, 9H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  158.4, 151.7, 146.4, 138.3, 117.1, 110.3, 3.0. 15

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CLAIMS

1. A compound of the formula



wherein A, B, D, E, and F are each independently nitrogen or carbon; R<sub>1</sub> is hydrogen, C<sub>1</sub> to C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>R<sub>7</sub>, or C<sub>1</sub> to C<sub>3</sub> alkyl-aryl; R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are each independently hydrogen, C<sub>1</sub> to C<sub>6</sub> alkyl, aryl, C<sub>1</sub> to C<sub>3</sub> alkyl-aryl, halogen, cyano, nitro, -(CH<sub>2</sub>)<sub>m</sub>NR<sub>8</sub>R<sub>9</sub>, -(CH<sub>2</sub>)<sub>m</sub>OR<sub>9</sub>, -SR<sub>9</sub>, -SO<sub>2</sub>NR<sub>8</sub>R<sub>9</sub>, -(CH<sub>2</sub>)<sub>m</sub>NR<sub>8</sub>SO<sub>2</sub>R<sub>9</sub>, -(CH<sub>2</sub>)<sub>m</sub>NR<sub>8</sub>CO<sub>2</sub>R<sub>9</sub>, -(CH<sub>2</sub>)<sub>m</sub>NR<sub>8</sub>COR<sub>9</sub>, -(CH<sub>2</sub>)<sub>m</sub>CONR<sub>7</sub>R<sub>9</sub>, or -(CH<sub>2</sub>)<sub>m</sub>CO<sub>2</sub>R<sub>9</sub>; R<sub>2</sub> and R<sub>3</sub>, R<sub>3</sub> and R<sub>4</sub>, R<sub>4</sub> and R<sub>5</sub>, and R<sub>5</sub> and R<sub>6</sub> may be taken together to form a five- to seven-membered alkyl ring, a six-membered aryl ring, a five- to seven-membered heteroalkyl ring, having 1 heteroatom of N, O, or S, or a five- to six-membered heteroaryl ring having 1 or 2 heteroatoms of N, O, or S; R<sub>7</sub> is -OR<sub>10</sub>, -SR<sub>10</sub>, -SO<sub>2</sub>NR<sub>10</sub>R<sub>11</sub>, -NR<sub>10</sub>SO<sub>2</sub>R<sub>11</sub>, -NR<sub>10</sub>CO<sub>2</sub>R<sub>11</sub>, -NR<sub>10</sub>COR<sub>11</sub>, -CONR<sub>10</sub>R<sub>11</sub>, or -CO<sub>2</sub>R<sub>10</sub>; R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub> and R<sub>11</sub> are each independently hydrogen, C<sub>1</sub> to C<sub>6</sub> alkyl, or C<sub>1</sub> to C<sub>3</sub> alkyl-aryl; m is 0, 1, or 2; n is 2, 3, or 4; and the above aryl groups and the aryl moieties of the above alkyl-aryl groups are each independently phenyl or substituted phenyl, wherein said substituted phenyl may be substituted with one to three of C<sub>1</sub> to C<sub>4</sub> alkyl, halogen, hydroxy, cyano, carboxamido, nitro, or C<sub>1</sub> to C<sub>4</sub> alkoxy, and the pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein B or E is nitrogen; A or F is carbon; R<sub>1</sub> is hydrogen, C<sub>1</sub> to C<sub>3</sub> alkyl, or -(CH<sub>2</sub>)<sub>2</sub>OCH<sub>3</sub>.

3. A compound according to claim 1, said compound being selected from:

- 30
- 3-(N-methylpyrrolidin-3-yl)-5-(pyrimid-5-yl)-1H-indole;
  - 5-(pyrimid-5-yl)-3-(pyrrolidin-3-yl)-1H-indole;
  - 3-[N-(2-methoxyethyl)pyrrolidin-3-yl]-5-(pyrimid-5-yl)-1H-indole;
  - 3-(N-ethylpyrrolidin-3-yl)-5-(pyrimid-5-yl)-1H-indole;

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5-(3-cyanopyrid-5-yl)-3-(N-methylpyrrolidin-3-yl)-1H-indole;

5-(3-cyanopyrid-5-yl)-3-(pyrrolidin-3-yl)-1H-indole;

5-(3-cyanopyrid-5-yl)-3-[N-(2-methoxyethyl)pyrrolidin-3-yl]-1H-indole; and

3-(N-methylpyrrolidin-3-yl)-5-(1,2,4-triazin-3-yl)-1H-indole.

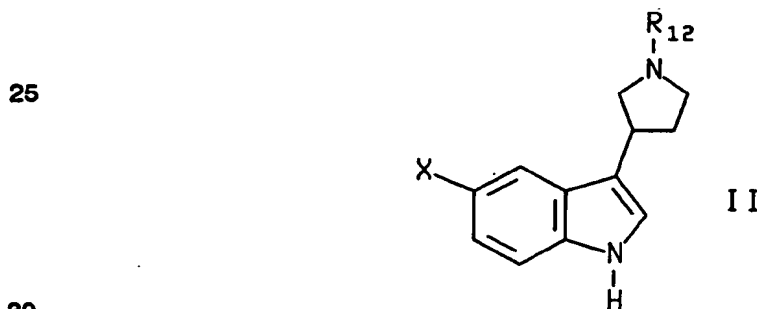
5 4. A pharmaceutical composition for treating a condition selected from hypertension, depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain, and chronic paroxysmal hemicrania and headache associated with vascular disorders comprising an amount of a compound according to claim 1 effective in treating such condition and a pharmaceutically acceptable carrier.

10 5. A pharmaceutical composition for treating disorders arising from deficient serotonergic neurotransmission comprising an amount of a compound according to claim 1 effective in treating such a disorder and a pharmaceutically acceptable carrier.

15 6. A method for treating a condition selected from hypertension, depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain, and chronic paroxysmal hemicrania and headache associated with vascular disorders comprising administering to a mammal requiring such treatment an amount of a compound according to claim 1 effective in treating such condition.

20 7. A method for treating disorders arising from deficient serotonergic neurotransmission comprising administering to a mammal requiring such treatment an amount of a compound according to claim 1 effective in treating such condition.

8. A compound of the formula



wherein X is halogen or -OSO<sub>2</sub>CF<sub>3</sub>, and R<sub>12</sub> is hydrogen, methyl, or benzyl.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/IB 94/00195

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D209/04 C07D401/04 C07D403/04 A61K31/40 /  
/(C07D403/04, 207:00, 209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,93 11106 (PFIZER) 10 June 1993 see whole document ---	1-7
Y	WO,A,91 18897 (THE WELLCOME FOUNDATION) 12 December 1991 cited in the application see whole document ---	1-7
X	WO,A,93 14087 (GLAXO) 22 July 1993 see example 1 (ii) see page 13 - page 14 ---	8
P,Y	WO,A,93 21178 (PFIZER) 28 October 1993 see whole document -----	1-7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

4 October 1994

Date of mailing of the international search report

19. 10. 94

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# INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/IB 94/00195

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9311106	10-06-93	AU-A- 2896192	28-06-93
		CA-A- 2124206	10-06-93
		FI-A- 942395	24-05-94
		PT-A- 101087	30-06-94
WO-A-9118897	12-12-91	AU-B- 646871	10-03-94
		AU-A- 7957091	31-12-91
		EP-A- 0486666	27-05-92
		JP-T- 5502679	13-05-93
		NZ-A- 238424	23-12-93
WO-A-9314087	22-07-93	AU-B- 3349893	03-08-93
WO-A-9321178	28-10-93	AU-B- 3952693	18-11-93